# Image-based modeling of tumor growth in patients with glioma.

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## 1 Introduction

In the diagnosis of brain tumors, extensive imaging protocols are routinely used to evaluate therapeutic options or to monitor the state of the disease. This gives rise to large numbers of multi-modal and multi-temporal image volumes even in standard clinical settings (Figure 1), requiring new approaches for comprehensively integrating information of different image sources and different time points. As all observations in these data sets arise from one underlying physiological process – the tumor-induced change of the tissue – a patient-specific model of tumor growth may provide new means for analyzing the acquired images and evaluating patient's options.

Mathematical tumor growth models try to explain the complex dynamics of cancer progression as a function of biological processes, which are assumed or known from prior experiments. Examples of such processes are the dynamics of individual tumor cells, their interactions with each other, their interactions with the surrounding tissue through mechanical or biochemical mechanisms or the generation, transport and allocation of substances relevant to specific biochemical processes.

In biomedical research, experiments may provide access to observables at the cellular level, e.g., to internal dynamics of cells, vascularization, and other factors such as acidity or cell-specific promoter substances. Consequently, tumors are often modeled at microscopic scale considering the dynamics at cellular level [1]. In clinical applications, the primary source of information is from medical images. Consequently, image-based tumor modeling matches the macroscopic scale. It describes the average behavior of tumor cells and macroscopic effects and general features at organ level, such as tumor invasion in white and gray matter, or the deformation of the brain due to the mass effect of the tumor.

While tumor modeling is well established in interpreting biomedical experiments, and is a tool for generating and testing hypothesizes about tumor processes and properties, little progress can be reported from clinical, personalized tumor modeling. Here, inferring personalized descriptors of disease or disease progression would potentially provide novel means for the quantification of tumor growth, staging of the disease, adaption of irradiation margin in radiation therapy planning, or the optimal dose application in chemotherapy.

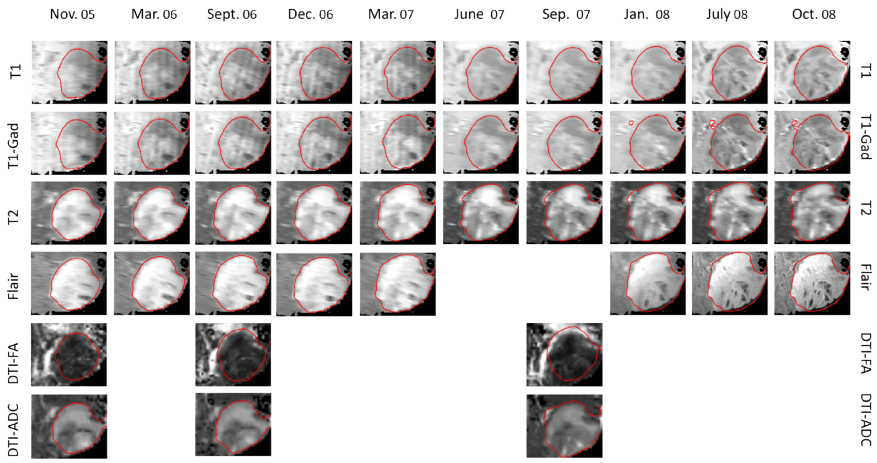


**Fig. 1.** Segmentation of the 44 MR volumes of a single patient with a glioma using a lesion-specific atlases for all ten time points of a multimodal image volume. Note that some modalities are missing for certain time points – which is a common problem in longitudinal studies. The tumor outlines are obtained using the latent atlas approach by Riklin-Raviv et al. [2, 3]

Evaluating image information using functional models of tumor growth can be stated as a problem of optimal control. We will review related work from the field of medical image analysis in this chapter. We will first describe general directions in the image-based modeling of tumor growth by highlighting a number of select studies (Section 2), and then point out standard applications of tumor models in the field of medical image processing (Section 3). Our overall application focus is on models of glioma, the most frequent and most aggressive of the primary brain tumors.

## 2 Image-based tumor modeling

The information available from an image observation, such as computed tomography scans, or magnetic resonance imaging, is at a macroscopic scale – with typical spatial resolutions at the millimeter level. Among the tumor-induced processes visible at this scale, two effects are most prominent: changes in tissue properties resulting from the invasion of healthy tissue by tumor cells, and the displacement of tissue resulting from tumor growth. Visible from images in clinical imaging protocols are, for example, differences in the amount of tissue water ($T_2$, Flair-MRI), in the diffusivity of water (DTI) or blood (DCE-MRI), the integrity of the blood-brain barrier (post-Gadolinium $T_1$-MRI), or changes in the relative concentrations of selected metabolites (MRSI). Displacements can be observed in any modality with sufficient resolution and tissue contrasts. As a consequence, image-based tumor models can be grouped into two classes: models

that concentrate on the migration of tumor cells and their invasive processes, and models that consider the mechanical mass effect of the lesion and their imprint on surrounding tissues.

A particular problem in image-based tumor modeling is the estimation of patient-specific and disease-specific model parameters, i.e., in inverting the forward model equations. Few studies address this difficulty, as Hogea et al. do in [4] using a registration framework, or even present models which are consistent with the observed information, such as Konukoglu's approach [5] based on a preceding tumor segmentation (Figure 2).

### 2.1 Reaction-diffusion models of cell invasion

The majority of all macroscopic glioma models use the reaction-diffusion formalism [6]. In particular the Fisher-Kolmogorov model – very generally describing the dynamics of invasive populations – enjoys popularity as a simplified model of tumor growth.

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + R(u,t) \tag{1}$$

where $u$ is the tumor cell density, $\partial u/\partial t$ is the differentiation operator with respect to time, $D$ is the diffusion tensor for tumor cells, which can be a function of location $x$, and $R(u,t)$ is the reaction term.

This partial differential equation models changes in a continuous tumor cell density $u$ by two individual processes considering cell migration and cell doubling. The first term on the right-hand side, $\nabla \cdot (D \nabla u)$, describes the invasion of tumor cells as a diffusive flux along the concentration gradient (Fick's diffusion). This process is characterized by the diffusion tensor $D$. The second term in the equation, $R(u,t)$, describes the cell doubling, or proliferation, of tumor cells as a function of the current cell concentration. Common population growth equations for this reaction term are exponential, logistic and Gompertian. Exponential growth models use $R(u,t) = \rho \cdot u$ and are valid for low tumor cell concentrations, with $\rho$ being the proliferation constant determining cell doubling. Logistic and Gompertian reaction terms represent self-limiting growth, with $R(u,t) = \rho \cdot u \cdot (1-u)$ and $R(u,t) = \rho \cdot u \ln(1/u)$, respectively.

In addition to the general, functional description on tumor cell evolution governed by eq. (1), there are no-flux boundary conditions such as

$$\eta \cdot (D \nabla u) = 0 \tag{2}$$

introducing additional structural information on the patient-specific shape and geometry of the brain. These boundary conditions consider that tumor cells will only migrate within white and gray matter tissues along normal directions $\eta$ of boundaries to other tissues. Tissue boundaries are derived from a preceding tissue segmentation in a patient-specific manner.

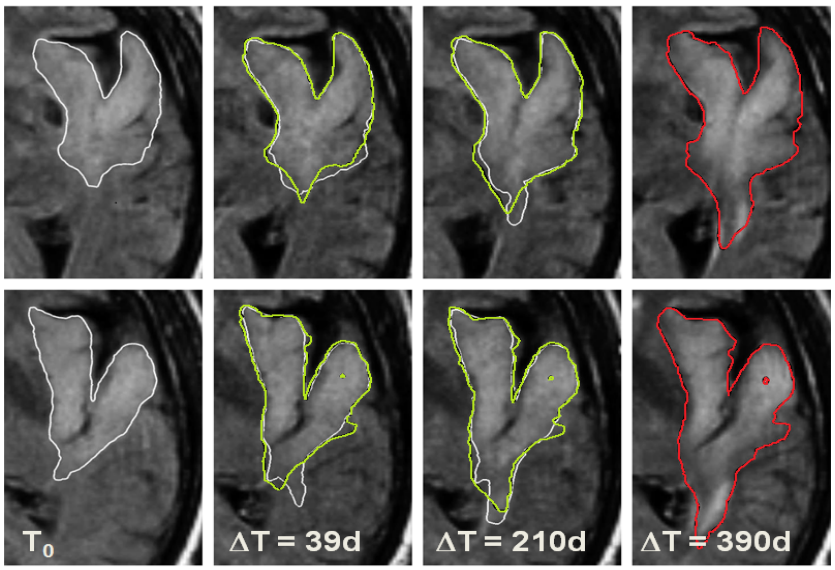


**Fig. 2.** Three-dimensional evolution of tumor growth and the prediction of tumor development for a patient with a low grade glioma, using the model approximation of Konukoglu et al. [5]. Shown are two FLAIR-MRI image slices (top and bottom row) with manual tumor delineations (white) used to parameterize the growth model. Green outlines in column two and three represent results from fitting the model to observations one to three. Red outlines in the final, forth column represent an extrapolation of the parameterized tumor model by 180 days beyond the third observation. Predictions are in good accordance with the true evolution of the tumor.

An early study proposing to use a reaction-diffusion framework for modeling tumor growth in patients with gliomas was Cruywagen et al. in [7]. They included the effect of treatment as another, negative reaction term $R(u,t)$ in eq. (1). In this model the invasion of tumor cells is assumed to be isotropic, following a homogeneous diffusion, i.e., with $D$ being a global scalar value.

In a subsequent study, and motivated by experimental results of Giese et al. [8], Swanson et al. [9] proposed to improve on this model by assuming nonhomogeneous diffusion. To consider the differential motility of tumor cells in gray and white matter, they replaced the diffusivity constant $D$ by an isotropic but nonhomogeneous diffusion coefficient $D(x)$. $D(x)$ took on two different values in the white matter, $d_w$, and in the gray matter, $d_g$, where $d_w \ll d_g$ acknowledges the observation that tumor cells move faster in white matter. In [10], they later also included the effect of chemotherapy, again by using a negative reaction term $R(u,t,x)$ in eq. 2.3. Here, the term is a function of both time and space, considering the time of drug delivery and the possible spatial heterogeneity of the drug efficacy. In their study, by comparing with real cases, the authors showed qualitatively that such models may successfully predict survival times.

Extending the idea of Swanson et al. [9], and refining on the differential motility of tumor cells in different tissues, Clatz et al. [11] and later Jbabdi et al. [12] proposed to use anisotropy to model the invasion mechanism of tumor cells. They modeled the diffusivity of tumor cells through an anisotropic-nonhomogeneous diffusion. The assumption they made is that tumor cells not only move faster in white matter, but also follow the white matter fiber tracts in the brain. This idea followed the observation that tumor cells tend to follow the preferred directions of water diffusion tensors $D(x)$, which can be measured using magnetic resonance diffusion tensor imaging (MR-DTI). These models were able to consider the resulting anisotropy in white matter diffusion and to capture the "spiky" and fingering patterns of tumors observed in the images. Both authors evaluate their models qualitatively by comparing visible tumors in the magnetic resonance images with the ones simulated with the model.

The general problem with the tumor model of eq. (1)-(2) is the observability of the modeled quantity $u$. While it describes the continuous evolution of tumor cell density $u$, these tumor cell densities cannot be observed from images directly. Konukoglu et al. [5] propose a parameter estimation method model that is consistent with the observed information in a standard MRI. For time series of medical images, they proposed to use the tumor delineation to identify correspondences between images acquired at different time points (Figure 2). To this end, Konukoglu et al. used a traveling wave approximation of the anisotropic and inhomogeneous reaction-diffusion model, eq. (1), to estimate a speed of growth that is parameterized by $D(x)$ and $\rho$. It is implemented with a fast parameter identification where

$$C = \frac{1}{2}[dist(\Gamma_2, \overline{\Gamma_2}), dist(\overline{\Gamma_2}, \Gamma_2)] \tag{3}$$

is the cost function to be minimized, based on two available tumor segmentations $\Gamma_2$ from time point $t_1$ and $\Gamma_1$ from time point $t_1$, and

$$\overline{\Gamma_2} = \{x | T(x) = t_2 - t_1, \sqrt{\nabla T D \nabla T} = \frac{1}{2\sqrt{\rho}}, T(\Gamma_1) = 0\} \tag{4}$$

is the optimization objective. $T(x)$ is an implicit time function that embeds the positions of the tumor delineation as an iso-time surface, i.e., it represents the time when the visible tumor border passes over the point $x$. Tumor growth is described by the Eikonal equation $\sqrt{\nabla T D \nabla T} = 1/(2\sqrt{\rho})$ derived from eq. (1), starting with the tumor segmentation $\Gamma_1$ available at time point $t_1$. Konukoglu uses an unconstrained optimization proposed by Powell [13] for estimating the model parameters. Modeling the front propagation as a traveling wave using the fast marching approach showed to be 2000 times faster than solving the reaction diffusion problem and, in a test for both low and high grade glioma patient data, showed good agreement with the actual development of the tumor (Figure 2).

### 2.2 Coupled bio-mechanical models of tissue displacement

The reaction-diffusion formalism, eqs. (1)-(2), models tumor growth as a reactive flow into a porous medium – with reactive tumor cells migrating into the surrounding, sponge-like tissues. In this model, tumor cells replace or transform healthy tissue, and the "mass effect" of newly generated cells is neglected. Bio-mechanical models explicitly consider this mass effect, model the interaction between tumor and its surroundings, and the displacement of the healthy tissue resulting from it. These models consist of two formal components: the tumor growth and the mechanical characteristics of the whole brain. Approaches have to make strong assumptions on the bio-mechanical properties of the brain, in particular on the elasticity and viscosity of the tissue, and the character of the mechanical coupling. A particular difficulty is in estimating parameters of the model from image information here, too.

Wasserman et al. [14] modeled brain tissue as a linear elastic material. The stress-strain relations are modeled by the generalized Hooke's law, and the amount of strain imposed on the tissue is proportional to the density of the tissue. For tumor growth, they assume an exponential growth rate, i.e., a constant cell doubling increase. They couple tumor and tissue model by assuming that pressure will be proportional to the volume of the neoplastic tissue.

Kyriacou et al. [15] improved on this by modeling brain tissue as an incompressible, hyper-elastic neo-Hookean material. Tumor growth is also modeled as an exponential process imposing the same strain as in [14]. They consider complex boundary conditions, and use their model to register patients with tumor-induced deformation to a standard tissue atlases.

Mohamed and Davatzikos [16] propose to model the brain tissue as an isotropic and homogeneous hyper-elastic material. They assume an exponential tumor growth, considering the mass effect caused by the edema surrounding the tumor. Pressure induced on the tissue by the tumor and edema is proportional

to the added volume. In [17], Hogea et al. reformulated the model with a level-set-based approach for the evolving tumor aiming at a more efficient method. They point out the use of patient-specific models with parameters estimated by solving an inverse problem.

Gevertz et al. [18] incorporated the impact that organ-imposed physical confinement and heterogeneity have on the tumor into their computational model. They show that models need to have organ geometry and topology in order to draw correct conclusions about tumor spread, shape and size. They also show that the impact that confinement has on the tumor growth is greater when the tumor is growing close to the confining boundary. They conclude that tumor models must consider shape, structure of organ and location of tumor within the organ to accurately predict the tumors growth dynamics.

### 2.3 Joint invasion and displacement models

Few approaches consider the invasion of tumor cells or tissue water ("edema"), and the displacement of the tissue resulting from the mass effect at the same time.

When introducing anisotropic nonhomogeneous diffusion for modeling tumor cell invasion in [11], Clatz et al. also considered tissue deformation due to bulk tumor growth. In their model brain tissue is modeled as a linear viscoelastic material in static equilibrium. Local pressure is caused by the mass effect both from tumor growth and the invasive process. With this model, they were able to simulate invasion and mass effect simultaneously.

Hogea et al. [4] use an optimal control framework to model the brain tissue as a piecewise linearly elastic material. The mass effect of tumor bulk and its infiltration are captured by a reaction-diffusion-advection model. Diffusion is isotropic as in [7]. The mechanical coupling is via the pressure field which is a parameterized function of the tumor cell density. The displacement is considered by complementing eq. (1) with an advection term:

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + \nabla (u \mathbf{v}) + \mathbf{R}(\mathbf{u}, \mathbf{t}) \tag{5}$$

with tumor cell drift $\mathbf{v}$. They also propose an adjoint-based, PDE-constrained optimization formulation for estimating model parameters from displacements visible in standard magnetic resonance images. They put forward two different objective functionals, matching the spatiotemporal evolution of the normalized tumor density $u(x, t)$ and landmark registration. Hogea conducted 1D experiments to show, for solving the optimization problem, the advantages of estimating the gradient of the objective functional in terms of the adjoints. The advantages are that there is only one solution required of the adjoint system (per optimization iteration) despite the number of inversion variables, and good scalability with regards to the number of control variables.

### 2.4 Modeling the response to therapy

Studies as [19, 10] propose simple approaches for considering the effect of therapy by using additional reaction terms in eq. (1). A large body of literature in optimal control considers drug delivery and reaction of tissue to radiation therapy. In general, however, these approaches do not aim at patient-specific optimization using image information, as in most cases the modeled quantities are not available at image scale. For modeling the temporal evolution of complex functional processes those approaches may use global information from chromatography, mass spectrometry, near infrared spectroscopy, and nuclear magnetic resonance spectroscopy instead. As a consequence, few models consider the spatial component in tumor evolution and inverse modeling.

One example estimating distributed parameters is Chakrabarty et al. [20], proposing an approach to optimizing drug delivery to brain tumors through an optimal control framed problem. Chakrabarty's goal is to minimize these tumor functionals with respect to the drug input rate, also considering physical restriction on the amount and costs of drugs that can be administered. This results in a coupled system of equations with a forward state equation and a backward costate equation that are solved using a modified double-shot, forward-backward method. They propose an algorithm to decide the optimal drug delivery using an optimal distribution of the drug about the initial tumor location, and they tested their model in 1D.

## 3 Tumor models in medical image analysis

A major field in medical image processing is three dimensional segmentation for localizing and quantitatively measuring anatomical structures of particular interest. The accurate segmentation of normal and tumorous tissues are also of crucial importance in personalizing tumor growth models. Here, generative models for both physiology and image appearance of tumors may serve the purpose of providing realistic,"ground truth" data sets to evaluate segmentation approaches.

Many tools for image segmentation have evolved around registration methods. Consequently, tumor models have been used repeatedly to address problems such as atlas-to-patient registration and segmentation in the presence of a lesion. In these cases pathological changes render standard atlases as useless, and using an appropriate tumor modeling framework allows one to adapt generative image models with respect to tissue displacements resulting from tumor growth. This increases the accuracy of image registration in the presence of extensive lesions.

### 3.1 Generative tumor models in image segmentation

Manual tumor segmentations show a high variability between raters. Different approaches may be used to infer a single, accurate segmentation from multiple tumor outlines [21]. This problem multiplies when multi-modal imaging sequences

are used and different tumor-induced changes become visible in the different modalities, demanding for robust automated segmentation approaches. Examples for such approaches are the level set-based segmentation by Riklin-Raviv et al. [2, 3] using a latent atlas prior for modeling the lesion (Figure 1), or the generative probabilistic model of both brain tissues and tumor segments by Menze et al., amending the standard EM segmentation with a similar prior to obtain tissue segmentations of both the healthy brain and the tumor outlines for every modality at the same time [22]. Accurately segmenting tumors in different modalities, however, remains a difficult task due to the high variability of tumor location, shape, and image texture. Here, tumor growth modeling can be used to synthetically generate both realistic tumor images, for different tumor types, tumor locations, in different modalities, and to provide quantitative "ground truth" segmentations for evaluating different tumor segmentation strategies, as in Kaster et al. [21].

Generating realistic appearing images has two components: it requires a model of the tumor growth process, and an image appearance model describing the effect of tumor growth on the image appearance, i.e., if and how tumor cell infiltrate the surrounding tissues, and if and how actively proliferating areas, edema and necrosis change the observed MR signal intensities.

Rexilius et al. [23] report one of the first approaches for such a synthetic image data generation. They use a basic tumor model with three compartments: the active tumor, the necrotic tumor core, and the edema in the surrounding tissue. The active tumor is manually drawn on the MR image of a healthy subject. A radial displacement model is adapted to fit its size and model the resulting displacement of the surrounding tissue, assuming linear elastic material properties for gray and white matter. The image intensities in the active and necrotic regions are modeled as Gaussian mixtures with predefined average and variance. Edema is modeled in the white matter with the intensity fading with increasing distance to the active tumor.

An approach for realistic MR images using a more sophisticated tumor growth model and an improved image appearance model has been developed by Prastawa et al.[24]. It is based on the tumor growth model by Clatz et al. [11] with extensions considering the displacement and destruction of white matter fibers in DTI-MRI, motivated by observations of Lu et al. [25]. They also model the dynamics of the contrast agent, its high-contrast accumulation in the cerebrospinal fluid and in the active tumor regions. For edema and active tumor regions, the image appearance is modified using characteristic image textures.

### 3.2 Generative tumor models in image registration

The registration of a patient's MRI with a large lesion to an anatomical atlas is a difficult task. An essential idea in this process, essential for example in the task of tissue segmentation, is to separate standard inter-subject variation of brain anatomy – captured in anatomical atlases, i.e., priors on the spatial distribution of the brain tissues – from the patient-specific, tumor-induced deformations.

Kyriacou et al. [15] propose a pipeline for correcting tumor-induced modifications of the normal anatomy. They simulate the resection of the tumor allowing images to be registered to a standard atlas and obtain a "tumor-free" image of the patient in a first step. Using these tumor-free images together with the real observations, they estimate parameters of a simple tumor growth model in a second step. The mass effect of the optimal tumor model is then used to modify the standard atlas, and to perform the final atlas-to-patient registration with subsequent segmentation.

In [26], Cuadra et al. proposed an approach requiring manual user interaction for identifying landmarks in the atlas and patient images. The tumor is modeled as a radial displacement on surrounding structures. The resulting displacement field is considered in a nonlinear registration using the "demons" registration algorithm.

Mohamed et al. [27] took a statistical approach jointly modeling normal and tumor-induced variation. They extend the idea of using atlases for variability between healthy subjects. They suggest to decompose the deformation field from a nonlinear registration into the natural variability between healthy subjects and the tissue displacements resulting from tumor growth. The formation fields of the normal brain are estimated from healthy subjects. Tumor growth is simulated by generating a space of displacement fields that results in tumor variation. The simulated tumor varies over different growth parameters, location and observed extent of tumor and edema. Once the deformation field linking the atlas to the subject and tumor growth parameters are found, the atlas is registered and the tumor is grown in it. An extension has been proposed by Zacharaki et al. [28].

## 4 Perspectives and further directions

In this chapter we summarized general approaches in the image-based modeling of tumor growth and pointed out studies of specific relevance in the design of these models. Most of these image-based approaches integrate image information into basic reaction-diffusion models, with or without coupling the tumor model and the displacement of the healthy tissues. These approaches are closely coupled to image registration and segmentation tasks. Major difficulties are in finding image descriptors which are consistent with the modeling framework – or, vice versa, a modeling framework that is consistent with the available image information – and in overcoming difficulties arising when approaches that showed to be useful in one or two dimensional examples are generalized to real clinical image data in 3D.

Further directions may be in developing more complex models of tumor growth, modeling nutrient, oxygen, and metabolite levels in the tumor, considering further structural model components of brain anatomy, or phenomena at the microscopic scale. Imaging modalities providing richer information than tumor outlines, such as positron emission tomography (PET), magnetic resonance spectroscopic imaging (MRSI) [29], diffusion contrast-enhanced MRI [30], functional-MRI (fMRI) [31], or other, even more specific molecular imag-

ing modalities may serve as the basis for such model extensions. A large body of studies on personalized management of tumor therapy, potentially to be used for such model extensions, is available from the field of theoretical biology and also frequently used in optimal control. Further work will be required to find principled, straightforward approaches for assimilating 3D image information into the bio-physical framework of those models.

Overall, the main prospect of image-based tumor modeling will be in quantitative personalized diagnostics and therapy optimization, but also in studying population statistics using novel computational descriptors of disease progression to be correlated, for example, with genetic descriptors to enhance the understanding of the disease.

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